UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/516,946	08/09/2005	Bernard Pau	263432US0XPCT	4965

22850 7590 02/22/2010

OBLON, SPIVAK, MCCLELLAND MAIER & NEUSTADT, L.L.P.
1940 DUKE STREET
ALEXANDRIA, VA 22314

EXAMINER
AEDER, SEAN E

ART UNIT	PAPER NUMBER
1642	

NOTIFICATION DATE	DELIVERY MODE
02/22/2010	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

patentdocket@oblon.com
oblonpat@oblon.com
jgardner@oblon.com

UNITED STATES PATENT AND TRADEMARK OFFICE

Commissioner for Patents
United States Patent and Trademark Office
P.O. Box 1450
Alexandria, VA 22313-1450
www.uspto.gov

BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

Application Number: 10/516,946
Filing Date: August 09, 2005
Appellant(s): PAU ET AL.

Thomas Cunningham
For Appellant

EXAMINER'S ANSWER

This is in response to the appeal brief filed 12/2/09 appealing from the Advisory Action mailed 10/13/09.

(1) Real Party in Interest

A statement identifying by name the real party in interest is contained in the brief.

(2) Related Appeals and Interferences

The examiner is not aware of any related appeals, interferences, or judicial proceedings which will directly affect or be directly affected by or have a bearing on the Board's decision in the pending appeal.

(3) Status of Claims

The statement of the status of claims contained in the brief is correct.

(4) Status of Amendments After Final

The appellant's statement of the status of amendments after final rejection contained in the brief is correct.

(5) Summary of Claimed Subject Matter

The summary of claimed subject matter contained in the brief is correct.

(6) Grounds of Rejection to be Reviewed on Appeal

The appellant's statement of the grounds of rejection to be reviewed on appeal is correct.

(7) Claims Appendix

The copy of the appealed claims contained in the Appendix to the brief is correct.

(8) Evidence Relied Upon

Maurer et al (Digestive Diseases and Sciences, 1998, 43(12): 2641-2648)

Macpherson et al (Proceedings of the American Association for Cancer Research Annual Meeting, 2002, 43:407-408)

Chao et al (J Exp Med, 1995, 182(3): 821-828)

Aggarwal et al (J Immunol, 1998, 160(4): 1627-1637)

(9) Grounds of Rejection

The following ground(s) of rejection are applicable to the appealed claims:

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1, 2, 5, 8, 10, 12, 24, and 27 remain rejected under 35 U.S.C. 103(a) as being unpatentable over Maurer et al (Digestive Diseases and Sciences, 1998, 43(12): 2641-2648) in view of Macpherson et al (Proceedings of the American Association for

Cancer Research Annual Meeting, 3/02, 43:407-408) and Chao et al (J Exp Med, September 1995, 182(3): 821-828) for the reasons set-forth below.

Maurer et al teaches a process comprising measuring the level of mRNA encoding Bax by detecting expression of an effector or marker gene expressing the pro-apoptotic Bax protein in a colorectal cancer cell from a subject having colorectal cancer, comprising detecting mRNA transcripts, wherein a probe or primer is used to detect the expression of the Bax gene, comprising contacting a nucleotide probe for said effector or marker gene with a biological sample to be analyzed for a time and under conditions suitable for hybridization to occur and detecting hybridization (see Figure 2, in particular). Maurer et al further teaches expression of the BAX gene varies in colorectal cancer cells (see Figure 2, in particular).

Maurer et al does not specifically teach methods comprising determining the level of expression of BAX gene in cancer cells obtained from a patient and comparing the level with the level measured in a corresponding control sample of cells not resistant to oxaliplatin. However, these deficiencies are made up in the teachings of Macpherson et al and Chao et al.

Macpherson et al teaches reduced expression of Bcl-xl in colon cancer cells, as compared to control cells wherein Bcl-xl expression was not reduced, results in an enhanced apoptotic response to oxaliplatin (see abstract).

Chao et al teaches Bcl-xl and Bcl-2 function as repressors of apoptosis by heterodimerizing with and inhibiting pro-apoptotic BAX (page 821 and page 826, in particular).

One of ordinary skill in the art at the time the invention was made would have been motivated to perform a method of detecting resistance of a cancer cell to oxaliplatin treatment by determine the level of expression of BAX gene in cancer cells obtained from the patient and comparing the level with the level measured in a corresponding control sample of cells not resistant to oxaliplatin when performing the method of Maurer et al because Macpherson et al teaches reduced expression of Bcl-xl, a repressor of apoptosis that functions by inhibiting BAX (see pages 821 and 826 of Chao et al), in colon cancer cells results in an enhanced apoptotic response to oxaliplatin (see abstract of Macpherson et al). Therefore, colorectal cancer cells with less BAX expression detected in the method of Maurer et al would be expected to be more resistant to oxaliplatin than cells with higher levels of BAX expression because apoptosis of colorectal cancer cells by oxaliplatin has been shown to be inhibited by a reduction in expression of Bcl-xl, Bcl-xl functions as a repressor of apoptosis by heterodimerizing with and inhibiting pro-apoptotic BAX, and the pro-apoptotic function of BAX would be diminished in colorectal cancer cells with lower levels of BAX that were treated with oxaliplatin (just as the anti-apoptotic function of Bcl-xl, due to heterodimerization and inhibition of BAX, is diminished in colorectal cancer cells with lower Bcl-xl expression treated with oxaliplatin). One of ordinary skill in the art at the time the invention was made would have had a reasonable expectation of success for performing a method of detecting resistance of a cancer cell to oxaliplatin treatment by determine the level of expression of BAX gene in cancer cells obtained from the patient and comparing the level with the level measured in a corresponding control sample of

cells not resistant to oxaliplatin when performing the method of Maurer et al because Macpherson et al teaches reduced expression of Bcl-xl, a repressor of apoptosis that functions by inhibiting BAX (see pages 821 and 826 of Chao et al), in colon cancer cells results in an enhanced apoptotic response to oxaliplatin (see abstract of Macpherson et al). Therefore, colorectal cancer cells with less BAX expression detected in the method of Maurer et al would be expected to be more resistant to oxaliplatin than cells with higher levels of BAX expression because apoptosis of colorectal cancer cells by oxaliplatin has been shown to be inhibited by a reduction in expression of Bcl-xl, Bcl-xl functions as a repressor of apoptosis by heterodimerizing with and inhibiting pro-apoptotic BAX, and the pro-apoptotic function of BAX would be diminished in colorectal cancer cells with lower levels of BAX that were treated with oxaliplatin (just as the anti-apoptotic function of Bcl-xl, due to heterodimerization and inhibition of BAX, is diminished in colorectal cancer cells with lower Bcl-xl expression treated with oxaliplatin) Therefore, the invention as a whole would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made, absent unexpected results.

Claims 1, 2, 5, 8, 10-12, 24, and 27 remain rejected under 35 U.S.C. 103(a) as being unpatentable over Maurer et al (Digestive Diseases and Sciences, 1998, 43(12): 2641-2648) in view of Macpherson et al (Proceedings of the American Association for Cancer Research Annual Meeting, 3/02, 43:407-408) and Chao et al (J Exp Med, September 1995, 182(3): 821-828) as applied to claims 1, 2, 5, 8, 10, 12, 24, and 27

above, and further in view of Aggarwal et al (J Immunol, February 1998, 160(4): 1627-1637) for the reasons set-forth below.

The combined teaching Maurer et al, Macpheron et al, and Chao et al are discussed above.

The combined teachings of Maurer et al, Macpheron et al, and Chao et al do not specifically teach a method comprising obtaining a cDNA from the RNA of the biological sample and amplifying the cDNA using at least one primer for amplification of BAX. However, this deficiency is made up in the teachings of Aggarwal et al.

Aggarwal et al teaches a quantitative PCR method comprising obtaining a cDNA from RNA of a biological sample and amplifying the cDNA using at least one primer for amplification of BAX (Figure 7, in particular).

One of ordinary skill in the art at the time the invention was made would have been motivated to use a quantitative PCR method comprising obtaining a cDNA from RNA of a biological sample and amplifying the cDNA using at least one primer for amplification of BAX when detecting the expression of BAX in the combined method of Maurer et al, Macpheron et al, and Chao et al because the quantitative PCR method of Aggarwal et al would provide quantitative results for determining BAX expression in the combined method of Maurer et al, Macpheron et al, and Chao et al. One of ordinary skill in the art at the time the invention was made would have had a reasonable expectation of success for using a quantitative PCR method comprising obtaining a cDNA from RNA of a biological sample and amplifying the cDNA using at least one primer for amplification of BAX when detecting the expression of BAX in the combined

method of Maurer et al, Macpheron et al, and Chao et al because Aggarwal et al teaches primers that amplify BAX cDNA and methods of using said primers to amplify BAX cDNA (page 1628, in particular). Therefore, the invention as a whole would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made, absent unexpected results.

(10) Response to Argument

Issue A: Rejection under 35 U.S.C. 103(a)

Appellant argues that none of the cited references suggest that a reduced level of expression of Bax gene alone correlates with enhanced resistance to oxaliplatin. Appellant further argues that the Examiner has not clearly articulated reasons why the invention would have been obvious to one of ordinary skill in the art at the time of invention. Appellant further argues that based on Chao et al, the person of ordinary skill would have used the ratio of heterodimer pair Bcl-2/Bax compared to unbound Bax rather than comparative levels of Bax and/or Bak expression alone to attempt to determine oxaliplatin resistance in a cancer cell. Appellant stresses that Chao et al is silent about whether Bax gene alone correlates with oxaliplatin resistance. Appellant further states that, based on Chao et al, a high level of Bax expression in a cancer cell could correlate with oxaliplatin resistance if the Bcl-xl level in the cancer cell leads to heterodimerization of all the Bax protein and inhibition of apoptosis. Appellant further states that, based on Chao et al, if the level of expression of Bax is weak and the Bcl-xl expression level is weaker, then there will be free Bax (not heterodimerized with Bcl-xl)

and a weak level of Bax is not necessarily correlated with an enhanced resistance to oxaliplatin.

These arguments have been carefully considered, but are not deemed persuasive. In regards to the argument that none of the cited references suggest that a reduced level of expression of Bax gene alone correlates with enhanced resistance to oxaliplatin, a reduced level of expression of Bax gene correlating with enhanced resistance to oxaliplatin is rendered obvious by the cited references. Specifically, Macpherson et al teaches reduced expression of Bcl-xl, a repressor of apoptosis that functions by inhibiting BAX (see pages 821 and 826 of Chao et al), in colon cancer cells results in an enhanced apoptotic response to oxaliplatin (see abstract of Macpherson et al). Therefore, colorectal cancer cells with less BAX expression detected in the method of Maurer et al would be expected to be more resistant to oxaliplatin than cells with higher levels of BAX expression because apoptosis of colorectal cancer cells by oxaliplatin has been shown to be inhibited by a reduction in expression of Bcl-xl, Bcl-xl functions as a repressor of apoptosis by heterodimerizing with and inhibiting pro-apoptotic BAX, and the pro-apoptotic function of BAX would be diminished in colorectal cancer cells with lower levels of BAX that were treated with oxaliplatin (just as the anti-apoptotic function of Bcl-xl, due to heterodimerization and inhibition of BAX, is diminished in colorectal cancer cells with lower Bcl-xl expression treated with oxaliplatin).

In regards to the argument that the Examiner has not clearly articulated reasons why the invention would have been obvious to one of ordinary skill in the art at the time of invention, the Advisory Action of 10/13/09 clearly articulated such reasons.

In regards to the argument that based on Chao et al, the person of ordinary skill would have used the ratio of heterodimer pair Bcl-2/Bax compared to unbound Bax rather than comparative levels of Bax and/or Bak expression alone to attempt to determine oxaliplatin resistance in a cancer cell, this rejection is not based solely on Chao et al. Further, reasons for comparing levels of Bax to determine oxaliplatin resistance in a cancer cell are discussed above. *Further*, a method comprising determining the ratio of the pair Bcl-xl/Bax as compared to unbound Bax in cancer and oxaliplatin resistant cells (a method which Appellant considers obvious from the cited references) requires detecting the expression of Bax in cancer and oxaliplatin resistant cells and comparing expression of Bax in cancer and oxaliplatin resistant cells. Such a method anticipates the instant claims. The instant claims are not limited to methods which only detect Bax or Bak.

In regards to the argument that based on Chao et al, a high level of Bax expression in a cancer cell could correlate with oxaliplatin resistance if the Bcl-xl level in the cancer cell leads to heterodimerization of all the Bax protein and inhibition of apoptosis, this rejection is not based solely on Chao et al. Based on the cited references, a high level of pro-apoptotic Bax would be indicative of sensitivity to oxaliplatin. Colorectal cancer cells with high BAX expression detected in the method of Maurer et al would be expected to be less resistant to oxaliplatin than cells with lower

levels of BAX expression because apoptosis of colorectal cancer cells by oxaliplatin has been shown to be inhibited by a reduction in expression of Bcl-xl, Bcl-xl functions as a repressor of apoptosis by heterodimerizing with and inhibiting pro-apoptotic BAX, and the pro-apoptotic function of BAX would be greater in colorectal cancer cells with higher levels of BAX that were treated with oxaliplatin (just as the anti-apoptotic function of Bcl-xl, due to heterodimerization and inhibition of BAX, is greater in colorectal cancer cells with higher Bcl-xl expression treated with oxaliplatin).

In regards to the argument that based on Chao et al, if the level of expression of Bax is weak and the Bcl-xl expression level is weaker, then there will be free Bax (not heterodimerized with Bcl-xl) and a weak level of Bax is not necessarily correlated with an enhanced resistance to oxaliplatin, this rejection is not based solely on Chao et al. Based on the cited references, cells with a weaker level of BAX expression detected in the method of Maurer et al would be expected to be more resistant to oxaliplatin than cells with higher levels of BAX expression because apoptosis of colorectal cancer cells by oxaliplatin has been shown to be inhibited by a reduction in expression of Bcl-xl, Bcl-xl functions as a repressor of apoptosis by heterodimerizing with and inhibiting pro-apoptotic BAX, and the pro-apoptotic function of BAX would be diminished in colorectal cancer cells with lower levels of BAX that were treated with oxaliplatin (just as the anti-apoptotic function of Bcl-xl, due to heterodimerization and inhibition of BAX, is diminished in colorectal cancer cells with lower Bcl-xl expression treated with oxaliplatin).

For the above reasons, it is believe that the rejection should be sustained.

Issue B: Rejection under 35 U.S.C. 103(a)

Appellant states that Aggarwal et al does not remedy alleged deficiencies of the other applied references.

For the above reasons, it is believe that the rejection should be sustained.

(11) Related Appeals and Interferences

No decision rendered by a court or the Board is identified by the examiner in the Related Appeals and Interferences section of this examiner's answer.

For the above reasons, it is believed that the rejections should be sustained.

Respectfully submitted,

/Sean E Aeder/

Primary Examiner, Art Unit 1642

Conferees:

/Larry R. Helms/

Supervisory Patent Examiner, Art Unit 1643

/Gary B. Nickol /

Supervisory Patent Examiner, Art Unit 1646